The discovery of mutations in the SCN9A gene, encoding the sodium channel Na\textsubscript{v}1.7, have revealed a wide spectrum of clinical phenotypes and determined the aetiologies of a number of clinical syndromes. This includes primary erythromelalgia, congenital insensitivity to pain, paroxysmal extreme pain disorder and small fibre neuropathy (Fischer and Waxman, 2010; Liu and Wood, 2011). Genetic analysis of the SCN9A gene has become an important diagnostic test in the characterisation of pain syndromes. The study reported by Hoeijmakers and colleagues in this issue of Brain extends the Na\textsubscript{v}1.7 associated phenotype with the description of a family with pain, dysautonomia and small limbs (acromesomelia) (Hoeijmakers, 2012).

A number of sodium channels have been identified, but only seven (Na\textsubscript{v}1.1, Na\textsubscript{v}1.2, Na\textsubscript{v}1.3, Na\textsubscript{v}1.6, Na\textsubscript{v}1.7, Na\textsubscript{v}1.8 and Na\textsubscript{v}1.9) have been found to be expressed in the nervous system (Dib-Hajj \textit{et al.}, 2010). Na\textsubscript{v}1.7 channels are preferentially expressed in nociceptive dorsal root ganglion and sympathetic neurons (Catterall and Yu, 2006). Na\textsubscript{v}1.7 appears to be important in early phases of neuronal electrogenesis and is characterized by slow transition of the channel into an inactive state when depolarized, allowing it to amplify small depolarizations such as generator potentials at the nerve endings of nociceptors. Na\textsubscript{v}1.7 therefore acts as a ‘gatekeeper’ within the peripheral pain-signalling pathway. The identification of mutations in the Na\textsubscript{v}1.7 gene has been a pivotal step in our understanding of pain and the role of the sodium channels (Cummins \textit{et al.}, 1998; Renganathan \textit{et al.}, 2001). With the addition of the pain, dysautonomia and acromesomelia syndrome described in this issue, the past 5 years have seen five human pain syndromes associated with Na\textsubscript{v}1.7 mutations.

Silas Weir Mitchell (1878) first described what we call erythromelalgia, from the Greek words erythros (red), melos (extremity) and algos (pain). In the initial case, he described idiopathic paroxysmal vasodilation of the peripheral vasculature marked by sudden onset of burning pain in the hands and feet. The fingers and toes usually become red with thickened terminal phalanges and nail beds, and superficial veins are grossly engorged. Over the last century, many similar cases have been reported (Smith, 1932; van Genderen, 1993; Davis, 2000; Layzer, 2001). Yang and colleagues (2004) identified mutations in Na\textsubscript{v}1.7 in two families from China with primary erythromelalgia. Further families from around the world were subsequently identified with heterozygous missense mutations, most frequently in domains I and II (5’ region of the gene). In this context, Na\textsubscript{v}1.7 mutations cause a hyperpolarizing shift in activation and slow deactivation, thus both opening the channel earlier and keeping it open longer once it is activated. Contributing to the hyperexcitability of pain-signalling dorsal root ganglion neurons expressing these mutant channels (Dib-Hajj \textit{et al.}, 2005; Drenth \textit{et al.}, 2005; Han \textit{et al.}, 2006; Fischer \textit{et al.}, 2009).

Paroxysmal extreme pain disorder, previously known as familial rectal pain, is an inherited condition first described by MacLennan (1917) as episodic rectal crisis or proctalgia fugax with intermittent attacks of sharp, severe, brief pain occurring in the region of the anorectal ring and the internal anal sphincter, typically occurring at defecation (Thaysen, 1935). In 1959, rectal, ocular and submaxillary pain (the full spectrum of paroxysmal extreme pain disorder) was described (Hayden and Grossman, 1959). The ocular pattern of pain is an intense burning sensation, followed by conjunctival injection and erythema of the eyelids and skin in the temporal region. There are often autonomic manifestations such as skin flushing and bradycardia (Dugan, 1972; Fertleman \textit{et al.}, 2006, 2007; Choi and Waxman, 2011). In 2006, a genome wide linkage analysis study was carried out in a large affected family. Genetic linkage was obtained to chromosome 2q24.3 and heterozygous missense mutations in Na\textsubscript{v}1.7 were identified mainly in domains III and IV (3’ region of the gene) (Fertleman \textit{et al.}, 2006). Functional analysis of a number of mutations associated with paroxysmal extreme pain disorder has shown them to impair fast-inactivation without altering channel activation, leading to persistent current, prolonged action potentials and repetitive neuron firing in response to provoking stimuli, such as stretching and exposure to cold temperatures. The different effects of mutations in primary erythromelalgia (which enhance channel activation) and paroxysmal extreme pain disorder (which impair channel inactivation) might contribute in part to the different symptomatology in these two disorders. In either case, these results are in keeping with the notion that Na\textsubscript{v}1.7 plays a critical role in modulation of the pain threshold (Dib-Hajj \textit{et al.}, 2008; Jarecki \textit{et al.}, 2008). An extreme phenotype has been described in a child with
an A1632E mutation and overlapping clinical and electrical manifestations of primary erythromelalgia and paroxysmal extreme pain disorder, emphasizing the physiological continuum of these two conditions (Estacion, 2008).

A sensory neuropathy was first described by Leplat in 1846 when he reported a first single case of an ulcerating neuropathy under the title ‘mal perforant du pied’ (Leplat, 1846). Nélaton (1852) recognized the familial nature of this condition. True congenital insensitivity to pain was first described in a Bohemian man from Prague who appeared on the stage as ‘The Human Pincushion’ (van Ness Dearborn, 1932). Congenital insensitivity to pain is an autosomal recessive disorder where individuals have painless injuries beginning in infancy but otherwise all other sensory responses and the sensory nerves are normal upon examination. The complications of the disease follow the inability to feel pain with frequent descriptions of affected individuals walking over burning coals and putting spikes through their hands (Thrush, 1973). In 2006, Cox and colleagues described six patients stemming from three consanguineous families of northern Pakistani origin. They carried out homozygosity mapping identifying a locus on chromosome 2q24.3 and using a candidate gene approach identified homozygous nonsense mutations in SCN9A. These results have been confirmed in a number of other studies in families from around the world. Functional studies show that mutations associated with congenital insensitivity to pain cause loss of function of Na\textsubscript{1.7}. This is in contrast to the genetic basis of primary erythromelalgia and paroxysmal extreme pain disorder, in which the disorders result from heterozygous gain-of-function missense mutations (Ahmad et al., 2007; Cox et al., 2010; Goldberg et al., 2007).

In two recent studies, Na\textsubscript{1.7} mutations have been found in patients with non-paroxysmal small fibre neuropathy (Dabby, 2011; Faber et al., 2011). The onset is late, identified at ages 14–68 years. In most patients, pain begins distally (feet > hands), some patients experience generalized pain with myalgia before developing distal pain, and some develop autonomic problems. The identified Na\textsubscript{1.7} defects are heterozygous missense mutations. The electrophysiological features were gain-of-function with impairment of slow inactivation, depolarized slow and fast inactivation, or enhanced resurgent currents. None of these mutations showed the hyperpolarized activation of primary erythromelalgia or impaired fast inactivation of paroxysmal extreme pain disorder.

In the new study by Hoeijmakers and colleagues (2012), a unique Dutch kindred is described with the clinical features of small fibre neuropathy and erythromelalgia, together with a remarkable phenotype of small forearms, hands, lower legs and feet (acromesomelia). The proband presented at 10 years of age with erythromelalgia and some years later developed burning pain in his hands triggered by warmth, relieved by cold water, and later significant autonomic problems. Examination and nerve conduction studies were normal but thermal thresholds and skin biopsy consistent with a small fibre neuropathy. His father had redness of the feet and hands that resolved after his twenties and one brother had paroxysmal redness, painful limbs and intermittent autonomic features. All three had small under-developed acral and distal limbs as compared with their unaffected brother, mother and general population, suggesting that the association with Na\textsubscript{1.7} is real rather than co-incidental. The three affected individuals in this family all harboured a novel mutation in Na\textsubscript{1.7} (c.2567G>A; G856D) not present in controls and located in domain II of the Na\textsubscript{1.7} protein, close to several other mutations that cause primary erythromelalgia and small fibre neuropathy. Like most inherited erythromelalgia mutations described, G856D hyperpolarizes the voltage-dependence of activation and slows deactivation. Unlike other mutations seen with primary erythromelalgia, paroxysmal extreme pain disorder and small fibre neuropathy, the G856D mutation produces a dramatic increase in persistent current. The Waxman group has characterized many defects in this channel and its electrophysiological phenotype (Fig. 1).

This family has the clinical phenotype, segregating Na\textsubscript{1.7} mutation type and localization, and the patch clamp functional properties that combine those seen in primary erythromelalgia and small fibre neuropathy (Drenth and Waxman, 2007). The small limbs segregating with the disease are so far unique to the G856D Na\textsubscript{1.7} mutation but our knowledge of Na\textsubscript{1.7} beyond pain is still evolving, as exemplified by the recent identification...
of loss-of-function Na\textsubscript{v}1.7 defects associated with anosmia (Waxman, 2011; Weiss et al., 2011). Limb morphogenesis is complex and has been associated with several gene mutations that cause syndromal and non-syndromal limb defects. None of these genetic defects are associated with a significant neuropathy or pain phenotype. In addition small limbs are not a feature of the inherited sensory neuropathies or Charcot–Marie–Tooth disease, suggesting this is a unique feature to this particular Na\textsubscript{v}1.7 mutation or the closely localized region (Dyck, 1993). The role of sodium channels in limb development is not understood. Na\textsubscript{v}1.7 has not been reported to be expressed in bone or cartilage cells at any stage of development, but transient expression may occur and affect limb development (Black et al., 1995; Sangameswaran et al., 1997). A more plausible explanation is that the mutation causes abnormal function of small-diameter axons innervating the limb leading to altered vasomotor function (Rush et al. 2006). It is also unknown how the G856D Na\textsubscript{v}1.7 mutation causes limb abnormalities as opposed to other mutations. Na\textsubscript{v}1.7 is important for dendrite cell migration, and G856D is in a region that may interact with Na\textsubscript{v}1.4 (Theile and Cummins, 2011), which is important for cell-cell adhesion and migration (Brackenbury and Isom, 2011). Further proof may be obtained if a mouse model could be developed targeted to this and other mutations in this region. A number of disorders are known to cause a neuropathy and abnormal limb development in utero. The most notable of these is that associated with the drug thalidomide (Holmes, 2002; Vargesson, 2009), where a small number of patients treated with thalidomide mainly for graft versus host disease, developed a sensory neuropathy with painful paraesthesias or numbness. Phacomelia is associated with thalidomide, in children of mothers who had taken this drug while pregnant in the 1960s but few patients have been assessed later in life for pain and neuropathy. It is possible that certain Na\textsubscript{v}1.7 mutations or even polymorphisms are found in the patients with limb abnormalities associated with maternal thalidomide use, or high doses may induce \textit{de-novo} events in this gene, as many thousands of mothers used thalidomide without complications (Reimann et al., 2010).

The genetic and physiological analysis of Na\textsubscript{v}1.7 in various types of pain syndrome has taught us a great deal about sodium channel function and pain. The description of this previously unreported condition in three individuals from the same family along with the segregating Na\textsubscript{v}1.7 mutation and unique channel characteristics is an important addition to our understanding of the normal role of Na\textsubscript{v}1.7. This report extends the Na\textsubscript{v}1.7 function beyond the pain syndrome into the pathway(s) involved in limb development.

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The deeper you look, the more you realize just how much we do not understand about pain. For those who favour the simple feed-forward model, three observations need to be considered. First, there is no ‘pain cortex’: even though regions light up beautifully and reproducibly in response to pain during functional brain imaging experiments, direct stimulation of any single cortical region fails reliably to reproduce the sensation of pain (see Mazzola et al., 2012: page 640 in this issue). Secondly, information travels the wrong way: a recent study of placebo analgesia showed modulation of activity primarily in the dorsal horn (Eippert...

The maladaptive brain: excitable pathways to chronic pain

As undergraduates, many of us were taught a simple and straightforward description of the anatomy and physiology of pain: the dorsal horn of the spinal cord receives nociceptive input from the periphery, which it transmits up the spinothalamic tract to the thalamus, which in turn gates and relays pain signals to the cerebral cortex where pain is ‘felt’. In this scheme, therefore, chronic pain should result from too much afferent input, or excess sensitivity to normal stimuli. But herein lies a problem: chronic pain rather too often occurs in the absence of any nociceptive input at all.

The better you look, the more you realize just how much we do not understand about pain. For those who favour the simple feed-forward model, three observations need to be considered.